REMARKS

The rejection of claims 42, 44, 55, 63, 65 and 69 under 35 USC Section 103(a) as being obvious over Hudziak *et al.* (US Patent No. 5,720,954) in view of Pauwels *et al. J. Pharm. Pharmacol.* 47(10): 870-875 (1995) is maintained. The Examiner dismisses Applicants earlier evidence of unexpected results as overcoming the 103 rejection. The Examiner urges that Applicant "has not provided any indication that the use of vinorelbine in combination with an anti-HER2 antibody would have shown any unexpected difference as compared to the use of a HER2 antibody in combination with other vinca drugs in the same family." The Examiner contends that the vinca alkaloid family appears to rely on the same mechanism of action, and that, therefore, one of ordinary skill in the art would expect that the use of any vinca alkaloid drug would have the same effect on the treatment of malignant disease.

Applicants rely on evidence of unexpected results as supporting the non-obviousness of the claims to rebut the Section 103 rejection. Such evidence includes the previously submitted Burstein *et al.* (2001) reference, and the Filipovich *et al.* (2002) abstract. Moreover, Applicants refer to Exhibit A attached which summarizes cytotoxicity data for the HER2 antibody Trastuzumab (HERCEPTIN®) and chemotherapy, including Vinorelbine (as recited in the presently pending claims of the above application) or Vinblastine (as set forth in the primary reference, Hudziak *et al.*). Exhibit A summarizes data from the following publications (also attached to this amendment): Pegram *et al. Oncogene* 18:2241-2251 (1999); Pegram *et al. Semin. Oncol.* 27(6) (suppl 11):21-25 (2000); Slamon and Pegram *Semin. Oncol.* 28(1) (Suppl 3): 13-19 (2001); and Hirsch *et al. Clin. Breast Cancer Suppl.* 3(suppl. 1): S12-S16 (2002). The data provides the Combination Index (CI) score from multiple drug-effect analysis at fixed molar ratios. (Lower CI scores correlate with a superior combination cytotoxicity). Whereas the HER2 antibody and **Vinblastine** referenced in column 6, line 64 of Hudziak *et al.* had an additive CI of **1.09**, the HER2 antibody and **Vinorelbine** species as recited in the claims of the present application had a **synergistic** CI of **0.34**. In fact, of the 16 different chemotherapies referenced in Exhibit A, Vinorelbine – the chemotherapeutic agent recited in the claims of the above application – had **the best CI**, 0.34, same as that achieved with the combination of Docetaxel and Carboplatin. Hence, Applicants submit that this further evidence demonstrates that the use of

Vinorelbine in combination with an anti-HER2 antibody results in an unexpected difference as compared to the use of a HER2 antibody in combination with the other vinca drug, Vinblastine, in the same family, being the species set forth in the cited primary reference, Hudziak *et al.* Moreover, Applicants submit that the Examiner's opinion that the vinca alkaloid family appears to rely on the same mechanism of action, and that, therefore, one would expect that the use of any vinca alkaloid drug would have the same effect on the treatment of malignant disease, is not substantiated, and contradicted by, the scientific data.

Applicants address above the primary reference, Hudziak *et al.*, which recites in column 6, line 64 cited by the Examiner the Vinblastine species of chemotherapeutic agent. As to the secondary reference, Pauwels *et al.*, while this discloses the Vinorelbine species of chemotherapeutic agent, it provides absolutely no motivation to combine such drug with a HER2 antibody as claimed in the present application. Nor does this secondary reference describe or allude to the unexpected results achieved with the HER2 antibody plus Vinorelbine combination as discussed above.

Applicants respectfully request reconsideration and withdrawal of the Section 103 rejection in view of the above comments. Applicants look forward to early notification of allowability of the above application.

Respectfully submitted,

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Date: December 16, 2005 By: WM Lee

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